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Reproducibility of Chronic and Acute Infarct Size Measurement by Delayed Enhancement-Magnetic Resonance Imaging

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OBJECTIVES The aim of this study was to evaluate the reproducibility of acute and chronic infarct size (IS) by delayed enhancement (DE) magnetic resonance imaging (MRI).

BACKGROUND Infarct size measurements can be used as surrogate end point to reduce the sample size in studies comparing different reperfusion strategies in myocardial infarction (MI). Delayed enhancement MRI is a rather new technique, and so far infarct IS reproducibility has not been established appropriately.

METHODS In 21 patients (10 acute MI and 11 chronic MI), IS was assessed repeatedly on consecutive days by DE-MRI. Reproducibility, interobserver, and intraobserver variabilities were assessed and compared by the Bland-Altman method.

RESULTS Acute and chronic IS were 17.1 ± 19.6% (range 5.1% to 69.8%) of LV mass (%LV) and 16.9 ± 9.9 %LV (range 2.0% to 36.0%), respectively. Infarct size difference (bias) between scan I and scan II was −0.5 %LV, and limits of agreement were ±2.4 %LV. Mean bias (−0.7 %LV) and limits of agreement (±3.2%) were slightly higher for acute in comparison with chronic MI with −0.4 ± 1.3 %LV. Intraobserver and interobserver variability was low with a mean bias of 0.3 %LV (limits of agreement ± 1.7 %LV) and −0.7 %LV (limits of agreement ± 2.2 %LV), respectively.

CONCLUSIONS Infarct size measurement by DE-MRI is an excellent tool for IS assessment, owing to its excellent repeatability in chronic and acute MI. It has therefore the potential to serve as a surrogate end point to uncover advantages of new reperfusion strategies. (J Am Coll Cardiol 2006;47:1641–5) © 2006 by the American College of Cardiology Foundation

Using mortality as a primary study end point in studies comparing different reperfusion strategies in acute myocardial infarction (MI) requires increasingly large sample sizes to test advances with existing therapies. Recently, there has been growing interest in infarct size (IS) measurements as a surrogate end point, allowing a much smaller sample size because of its prognostic value (1). There are several methods to assess IS, which include electrocardiography and imaging procedures such as single-photon emission computed tomography (SPECT) and echocardiography or the indirect assessment by the release of cardiac enzymes (2). Each of

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these methods, however, has its limitations. By echocardiography, IS can be estimated indirectly only by evaluation of left ventricular (LV) ejection fraction, regional wall motion, or end-systolic volumes (2). Single-photon emission computed tomography is hampered by attenuation artifacts and low spatial resolution, which does not allow for assessment of small infarcted areas (3). The measurement of cardiac enzyme release is influenced by several factors, such as the variability of normal serum concentrations and the effects of coronary reperfusion (4), thus rendering each of these methods a suboptimal tool for IS assessment.

Delayed enhancement (DE) magnetic resonance imaging (MRI) allows the direct visualization of infarcted or necrotic tissue at very high spatial resolution and is increasingly used to discriminate viable from non-viable myocardium (5–7). It may therefore be an optimal method to assess IS as surrogate end point for studies comparing different reperfusion strategies, if it can be assessed with low inter-study reproducibility. However, so far reproducibility of DE-MRI has been established only for chronic MI and for measurement within one day without a second contrast agent injection (2,8). The purpose of this trial was therefore to assess the reproducibility of acute and chronic IS measurements in patients scanned at subsequent days with a second contrast agent injection.

METHODS

Study population. Ten patients with first acute MI (range 1 to 3 days after the index event) and 11 patients with chronic MI (≥6 months) underwent two consecutive magnetic resonance scans on 2 consecutive days after written informed consent. All acute MI patients underwent primary percutaneous coronary intervention.

The study was approved by the local ethics committee. Patients were excluded from the study if they were hemodynamically unstable or had absolute or relative contraindi-

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Abbreviations and Acronyms

DE	= delayed enhancement
IR	= inversion-recovery
IS	= infarct size
LV	= left ventricle/ventricular
MI	= myocardial infarction
MRI	= magnetic resonance imaging
%LV	= percentage infarct size of left ventricular mass
SPECT	= single-photon emission computed tomography

cations for magnetic resonance examination, such as pacemakers and/or atrial fibrillation, among others. Furthermore, patients were excluded if they had history of previous MI or several chronic MI.

MRI. All patients were examined at rest in the supine position with a whole body 1.5-T MR scanner (Gyroscan Intera CV, Philips Medical Systems, Best, the Netherlands) equipped with a five-element cardiac phased-array coil for signal reception. A vectorcardiogram for gating and triggering was used. To define the orientation of the heart, a real-time interactive tool was applied. All images were acquired during breath-hold at endexpiration. Delayed enhancement short axis images covering the whole ventricle were acquired at enddiastole approximately 15 min (range 9 to 27 min) after bolus injection (0.2 mmol/kg/bodyweight) of Gadolinium-BOPTA (Gadovist, Schering, Germany). A three-dimensional inversion-recovery (IR) turbo gradient echo sequence (repetition time 2.8 ms, echo time 1.1 ms, flip angle 15°, typical spatial resolution 2.0 × 2.0 × 5 mm, two stacks, prepulse delay 175 to 300 ms) was used for image acquisition. The individual IR prepulse delay was defined to obtain the maximal contrast between viable and necrotic myocardium. For the second MR examination, the heart axes were newly defined by the interactive real-time tool. The IR prepulse delay was also newly defined, and care was taken to acquire DE images at the same time point after contrast injection.

Image analysis. Off-line image analysis was performed on an independent workstation with dedicated software. Image quality was assessed by a score ranging from 0 to 4 (0 = not assessable; 4 = optimal image quality). Left ventricular mass was assessed for the DE images by tracing the endocardial and epicardial contours manually; papillary muscles were included. Once the myocardial contours were identified, IS was determined by manual delineation of DE in each of the short axis images (Fig. 1). In patients with microvascular obstruction these dark areas were included for IS analysis (9). Infarct size was expressed as percentage of LV volume, given by the sum of the volume of DE regions for all slices divided by the sum of the LV myocardial cross-sectional volumes (%LV). All analyses were performed independently without any reference to the prior or the next day's images.

For assessment of interobserver variability in IS determination, the relevant datasets were analyzed by two independent observers. To determine intraobserver variability, analysis of all subjects was repeated after four weeks by one of the observers without reviewing the results of the first analysis.

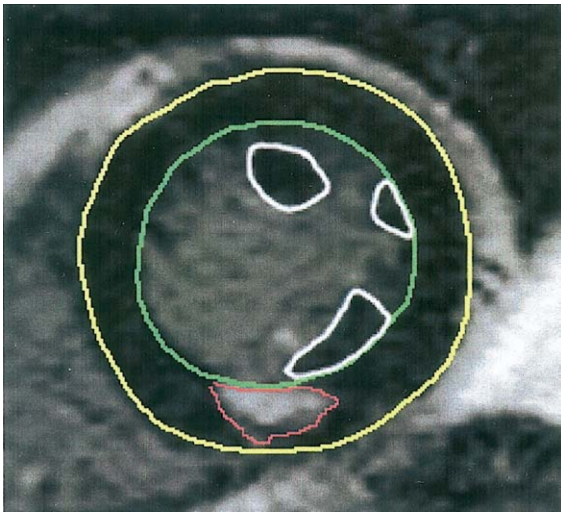

Figure 1. Short axis slice showing the endocardial **(green)**, epicardial **(yellow)**, papillary **(blue)**, and infarcted contours **(white)** in a patient with inferior myocardial infarction.

Statistical analysis. Continuous data are expressed as mean ± SD. The reproducibility of two measurements of the consecutive scans, degrees of agreement between different observers, and repeated measurements of one observer were determined as mean absolute difference (bias) and 95% confidence interval of the mean difference (limits of agreement) according to the methods of Bland and Altman (10).

RESULTS

The mean patient age was 59 ± 12 years (range 39 to 80 years); 17 patients were men, and 4 were women; 13 patients had anterior MI, and 8 had inferior MI. Image quality was appropriate in all patients to assess IS. Mean image quality was 3.1 ± 0.6 (range 2 to 4) for the DE images. In four acute MI patients, microvascular obstruction was present.

Mean IS for the overall patient population was 17.0 ± 14.9 %LV. In patients with acute MI, mean IS was 17.1 ± 19.6 %LV (range 5.1 to 69.8); and in those with chronic MI, mean IS was 16.9 ± 9.9 %LV (range 2.0 to 36.0). Table 1 summarizes technical parameters and MR IS of acute and chronic MI in all patients.

Reproducibility of MRI. Figure 2 shows the results of the Bland-Altman repeatability analysis of all patients. The average difference in IS measurement between scan I and scan II was −0.5 %LV and the limits of agreement were ±2.4 %LV. The mean bias (−0.7%) and the limits of agreement (±3.2 %LV) were slightly higher for acute in comparison with chronic IS with −0.4 ± 1.3 %LV. There were no systematic differences in IS between scan I and II and no differences for anterior and inferior MI.

Interobserver and intraobserver variability. Intraobserver and interobserver variability for IS assessment was low with

Table 1. Technical Parameters and Infarct Size Measured by MRI at Day 1, Day 2, and by Observer 2

			TI (ms)		Time After Contrast (min)		MRI			
Patient	Acute/ Chronic	Microvascular Obstruction	Scan I	Scan II	Scan I	Scan II	Day 1 %LV	Day 2 %LV	Day 1 %LV 2nd Assessment	Day 1 %LV Observer 2
1	Acute	−	300	300	17	18	5.1	5.0	4.9	6.0
2	Acute	+	225	250	17	18	19.7	16.7	20.5	20.2
3	Acute	−	225	225	16	17	5.7	5.5	5.3	6.0
4	Acute	−	275	250	20	20	13.8	15.8	14.1	14.2
5	Chronic	−	250	250	16	16	9.3	8.0	8.6	10.7
6	Chronic	−	225	225	17	18	18.0	18.4	17.3	19.7
7	Acute	−	250	250	17	15	5.4	5.4	5.5	6.1
8	Acute	+	175	175	18	18	69.8	67.3	68.7	66.2
9	Acute	−	250	250	16	13	5.6	6.0	5.5	6.4
10	Acute	+	200	225	10	10	21.7	19.0	22.4	23.9
11	Chronic	−	300	300	9	11	2.0	2.2	2.2	2.1
12	Chronic	−	210	200	10	10	29.5	28.6	29.1	31.2
13	Chronic	−	225	225	15	15	36.0	36.1	37.3	36.7
14	Acute	−	225	225	14	15	16.9	16.3	16.1	17.1
15	Acute	+	225	225	16	18	7.5	7.7	7.1	8.3
16	Chronic	−	225	230	15	17	18.2	17.1	15.8	19.0
17	Chronic	−	275	300	27	26	16.9	16.4	16.8	17.9
18	Chronic	−	225	225	13	13	4.1	4.8	4.5	4.6
19	Chronic	−	225	225	15	17	19.0	18.0	17.6	19.6
20	Chronic	−	250	250	18	17	18.2	18.0	18.1	18.6
21	Chronic	−	200	200	15	16	14.5	14.3	13.1	15.9

LV = left ventricle; MRI = magnetic resonance imaging; %LV = percentage infarct size of LV mass; TI = inversion time.

a mean bias of 0.3 %LV (limits of agreement ±1.7 %LV) and −0.7 %LV (limits of agreement ±2.2 %LV), respectively (Figs. 3A and 3B).

DISCUSSION

The main finding of this study is that reproducibility of MR IS assessment measured at consecutive days is excellent for acute and chronic anterior and inferior MI. In addition, the intraobserver and interobserver variability is low, making MRI the method of choice as a surrogate end point in clinical trials of reperfusion.

Reproducibility of MRI. Currently, only limited trials have assessed the reproducibility of MRI for IS assessment. Mahrholdt et al. (8) acquired images at two different time

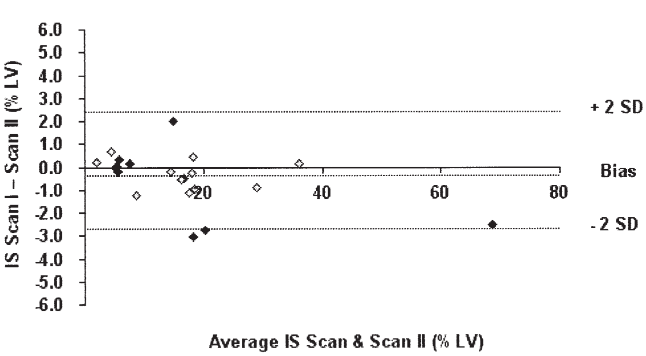

Figure 2. Bland-Altman reproducibility analysis for the overall patient population. **Central horizontal dotted line** = mean absolute difference or bias; **upper and lower lines** = 95% confidence intervals (limits of agreement); **black diamonds** = acute myocardial infarction (MI); **white diamonds** = chronic MI. IS = infarct size; %LV = percentage of LV volume.

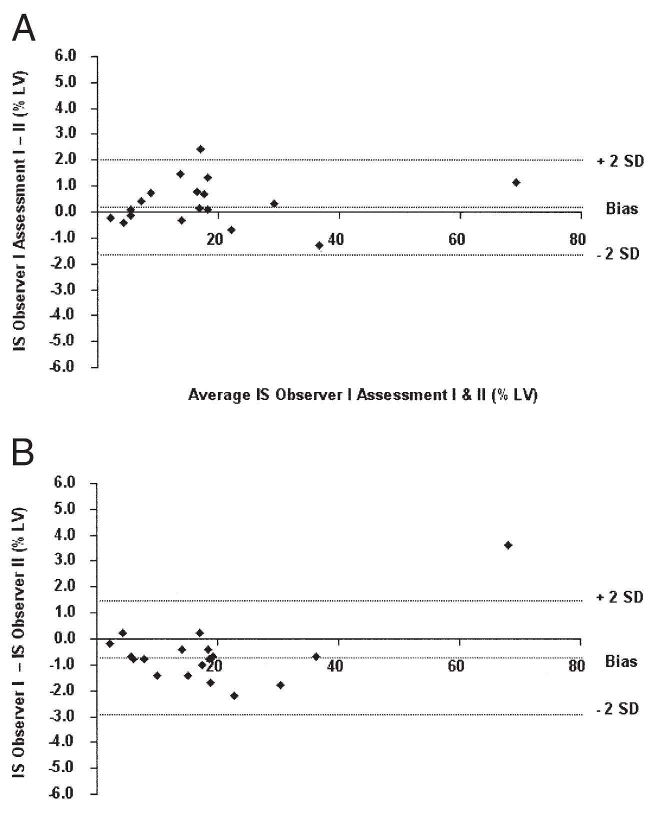

Figure 3. Bland-Altman analysis for intraobserver **(A)** and interobserver **(B)** variability. **Central horizontal dotted line** = mean absolute difference or bias; **upper and lower lines** = 95% confidence intervals (limits of agreement); **diamonds** = myocardial infarction (MI). Abbreviations as in Figure 2.

points (10 and 27 min). Their reproducibility data were similar to the current trial with a mean bias of −0.1 (limits of agreement ±2.4 %LV); however, this trial was restricted to chronic infarctions and to image acquisition after injection of a single contrast agent bolus. In another trial, 10 patients with chronic MI underwent repeated IS measurement 2 months apart. The apparent IS was not statistically different between the paired studies, although bias and limits of agreement were not reported (11). Therefore, the current trial is the first trial that assessed reproducibility in the acute and chronic MI setting with measurement at consecutive days with appropriate statistical methods.

Accurate infarct sizing by MRI. Another important factor besides reproducibility is the accuracy of infarct sizing. This can be affected by several factors. First, the time interval between contrast agent injection and image acquisition influences IS, if constant IR times (time between inversion prepulse and image acquisition) are used (12). Recent studies have shown, however, that by using appropriate inversion times to null normal myocardium, the time between contrast injection and image acquisition does not influence IS (8,13,14). Therefore, we prospectively designed the scan protocol to minimize inconsistent timing and used the best validated IR method (15), which was individually adapted to null normal myocardium in each patient and in each scan.

Image analysis is a crucial point for accurate IS assessment. Most studies have used arbitrary criteria for the definition of infarcted tissue. In some trials manual tracing of the enhanced region was performed (7,12), whereas in other trials semi-automatic computer-assisted algorithms were used (8,13,14,16). Recently, the most objective technique has been defined by the full-width at half-maximum criterion (13). This approach compared better with manual tracing and with an SD technique, which included hyperenhanced pixels with image intensities >1 to 6 standard deviations above the mean image intensity of remote myocardium (13). Nevertheless, manual tracing used in our study, which might be affected by subjective window setting, showed excellent repeatability results. These might even have been better by the use of the full-width at half-maximum criterion.

Furthermore, we had full volumetric coverage by using a three-dimensional IR sequence with two stacks acquired with two breath-holds. This minimizes chances of registration errors, which are inherent to a two-dimensional sequence acquiring each slice with a single breath-hold (17).

Delayed enhancement occurs in areas of expanded extracellular space, owing to slower distribution kinetics and higher regional Gadolinium concentration compared with normal myocardium. The theoretical pathologic basis in chronic MI is a result of fibrosis with subsequent increased extracellular space, whereas in acute MI, expansion of extracellular volume is deemed to be due to myocyte membrane disruption and increased capillary permeability (18). This different pathophysiological basis might explain the slightly better reproducibility in chronic compared with acute MI. In addition, the extent of microvascular obstruction, another rapidly changing factor in acute MI, might have influenced the IS reproducibility (19); however, because microvascular obstruction usually occurs in the subendocardial zone and because these areas have been included for IS analysis, this influence might be negligible.

Infarct size end point use in clinical trials. Single-photon emission computed tomography IS imaging has been used extensively as surrogate end point in clinical trials (2). An important advantage of SPECT is the ability to assess either salvaged myocardium by measuring both the acute and the final perfusion defect or the final IS. In contrast to the extensive experience with SPECT, to date there is only limited experience with use of DE-MRI as an end point in clinical trials. One early observational and one randomized study, using older imaging sequences, reported IS for patients with different reperfusion strategies in MI (20,21). Currently, there is only one randomized clinical trial using state-of-the-art IR sequences (22).

As a consequence of the limited use of DE-MRI, there are only very limited prognostic data in fewer than 50 patients (9). In this trial, patient outcome for a combined clinical end point was associated with the extent of final IS. Furthermore, MR infarct sizing is limited by non-standardized acquisition protocols and non-standardized quantitation. Therefore, multicenter comparability trials have not been performed thus far; however, owing to the high spatial resolution with ability to detect even very small subendocardial infarcts (23), more widespread availability in the future, and easier imaging protocols, these obstacles might be able to be overcome.

Sample size calculation. The reproducibility of an imaging procedure has practical implications for the sample size of clinical trials using IS as surrogate end point. The influence of measurement reproducibility is a function of the *t* statistic (24), which means that the number of patients required is proportional to the square of the standard deviation of the imaging end point as shown for SPECT (25). If IS is used as end point to show a change with a power of 90% and an alpha-error of 0.05, sample size calculations showed that (using the 1.2% standard deviation [0.5 limits of agreement] of MRI reproducibility in comparison with 4% standard deviation [0.5 limits of agreement] for recently published reproducibility data [8]) the required patient number can be reduced by 80% to 91%, depending on the expected absolute change in IS. This calculation, however, is made on the basis of a comparison with historical SPECT data, limited number of patients, and on the assumption that no other factors play a role in sample size calculation.

Study limitations. As a result of exclusion of patients with a previous MI and patients with atrial fibrillation, IS assessment was rather non-complex. Inclusion of patients with previous MI might have led to an impaired reproducibility, because delineation between previous and current MI might be more difficult. Furthermore, atrial fibrillation might impair image quality. Therefore, the current reproducibility data cannot be generalized to the entire population of patients with MI.

Conclusions. Infarct size measurement by DE-MRI is an excellent tool for acute and chronic MI owing to its high reproducibility and low intraobserver and interobserver variability. In comparison with other imaging modalities, it might allow a further sample size reduction and has therefore the potential to serve as a surrogate end point to uncover advantages of new reperfusion strategies in acute MI.

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